Mr. Hanumant Rananaware, 2026, 14:2
ISSN (Online): 2348-4098
ISSN (Print): 2395-4752

International Journal of Science, Engineering and Technology
An Open Access Journal

Synthesis, Spectral and Biological Studies of Transition Metal Complexes of 4-(2-(3-fluorobenzylidene) hydrazinyl)-7H-pyrrolo[2,3-d] pyrimidine

Mr. Hanumant Rananaware[1], Dr. M. A. Badgujar[2]

[1]Chemistry Dept., K. G. K. College, Karjat-Raigad.

[2]Dept of Chemistry, Shantarambhau Gholap Arts, Science and Gotirambhau Pawar Commerce College Shivle, Tal-Murbad, Dist-Thane, Maharashtra, India.

Abstract- A series of transition metal complexes of 4-(2-(3-fluorobenzylidene) hydrazinyl)-7H-pyrrolo[2,3-d]pyrimidine (L) were synthesized by reacting the ligand with metal salts of Fe(III), Cu(II), Co(II), Ni(II), and Zn(II) under reflux conditions. The complexes were characterized by various spectroscopic techniques, including UV-Vis, FTIR, NMR, and X-ray diffraction, which confirmed the coordination of metal ions to the ligand through the azomethine nitrogen and pyrimidine nitrogen. The electronic spectra revealed significant shifts in the absorption maxima upon complexation, indicating coordination-induced electronic changes. FTIR and NMR analyses further supported the bidentate nature of the ligand. Magnetic susceptibility and conductivity measurements suggested that the complexes exhibit low to moderate conductivity and a range of magnetic properties, consistent with the coordination environment of the metal ions. The antibacterial activity of the ligand and its metal complexes was evaluated against Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) bacteria using the disk diffusion method. The metal complexes exhibited superior antibacterial activity compared to the free ligand, with the Cu(II) and Co(II) complexes demonstrating the highest inhibition zones, particularly against E. coli. The increased activity of the metal complexes is attributed to enhanced membrane penetration and metal-ligand synergy, which likely alters the microbial cell's normal physiological processes. The results suggest that these complexes hold promise as potential antimicrobial agents, and further studies are warranted to explore their full therapeutic potential.

Keywords: Magnetic susceptibility, Conductivity measurements, Antibacterial activity, 4-Hydrazinyl-7H-pyrrolo[2,3-d]pyrimidine, 3-Fluorobenzaldehyde.

I. INTRODUCTION

The design and synthesis of transition metal complexes have been an area of considerable interest due to their diverse biological and catalytic properties. Transition metal ions, due to their unique electronic configuration, can effectively interact with ligands, leading to the formation of stable complexes that exhibit a range of biological activities, including antimicrobial, anticancer, and anti-inflammatory effects (Sharma et al., 2019; Roy et al., 2021). Pyrrolo[2,3-d]pyrimidine derivatives, in particular, have garnered significant attention due to their potential pharmaceutical applications. These compounds are known for their diverse pharmacological activities, including their ability to inhibit enzymes, modulate cell signaling pathways, and act as effective agents in the treatment of cancer and infectious diseases (Ali et al., 2020; Yadav et al., 2022).

The 4-(2-(3-fluorobenzylidene)hydrazinyl)-7H-pyrrolo[2,3-d]pyrimidine scaffold represents an intriguing structural motif that combines a pyrrolo[2,3-d]pyrimidine core with a hydrazine functional group. The incorporation of a fluorobenzylidene group further enhances the molecule's potential for coordination with metal ions, making it an ideal candidate for the formation of transition metal complexes. Studies have shown that metal coordination can significantly alter the physicochemical properties of ligands, potentially enhancing their biological efficacy (Ibrahim et al., 2018). Transition metal complexes of hydrazine-

based ligands have been widely studied for their improved antimicrobial and antitumor properties, suggesting that such complexes can offer superior therapeutic outcomes over their non-metal counterparts (Kumar et al., 2020).

The role of transition metals, such as copper, zinc, and nickel, in enhancing the biological activity of metal-ligand complexes is well-documented (Smith et al., 2021). Metal ions can influence the stability, reactivity, and solubility of the complexes, thereby affecting their ability to interact with biomolecules and perform therapeutic functions. In particular, the ability of metal complexes to bind to DNA, proteins, and other biomolecular targets has been extensively explored, revealing promising anticancer and antimicrobial potential (Sundararajan et al., 2019).

This study aims to synthesize and characterize transition metal complexes of 4-(2-(3-fluorobenzylidene)hydrazinyl)-7H-pyrrolo[2,3-d]pyrimidine, with a focus on their structural properties and biological activities. Spectroscopic techniques, such as UV-Vis, FT-IR, NMR, and X-ray diffraction, will be employed to confirm the formation of the metal complexes and assess their stability. Furthermore, the antimicrobial and cytotoxic activities of the synthesized complexes will be evaluated to determine their potential as therapeutic agents. By combining the biological efficacy of the pyrrolo[2,3-d]pyrimidine scaffold with the catalytic properties of transition metals, this work aims to contribute to the development of novel metal-based therapeutics with enhanced biological activities.

II. MATERIALS AND METHODS

Materials

All chemicals and solvents used in the synthesis and characterization of the compounds were purchased from commercial sources and used without further purification. The starting material, 4-(2-(3-fluorobenzylidene)hydrazinyl)-7H-pyrrolo[2,3-d]pyrimidine, was synthesized according to previously reported methods (Ali et al., 2020). The transition metal salts, such as copper(II) chloride ($CuCl_2$), zinc(II) acetate ($Zn(OAc)_2$), and nickel(II) chloride ($NiCl_2$), were purchased from Sigma-Aldrich and used as received. Solvents such as methanol, ethanol, dichloromethane (DCM), dimethyl sulfoxide (DMSO), and acetone were obtained from Merck and used for synthesis and characterization. All reagents and solvents were of analytical grade.

Synthesis of 4-(2-(3-fluorobenzylidene)hydrazinyl)-7H-pyrrolo[2,3-d]pyrimidine:

The ligand, 4-(2-(3-fluorobenzylidene)hydrazinyl)-7H-pyrrolo[2,3-d]pyrimidine, was synthesized by a condensation reaction between 4-amino-7H-pyrrolo[2,3-d]pyrimidine and 3-fluorobenzaldehyde in methanol under reflux conditions. A mixture of 4-amino-7H-pyrrolo[2,3-d]pyrimidine (1.0 mmol) and 3-fluorobenzaldehyde (1.0 mmol) was dissolved in 20 mL of methanol. The reaction mixture was heated for 4 hours at reflux. The resulting product was filtered, washed with cold ethanol, and dried under vacuum to obtain the desired ligand in high yield (Yadav et al., 2022).

Scheme 1: Synthesis of 4-(2-(3-fluorobenzylidene)hydrazinyl)-7H-pyrrolo[2,3-d]pyrimidine

Synthesis of Transition Metal Complexes:

To prepare the transition metal complexes, an appropriate metal salt ($CuCl_2$, $Zn(OAc)_2$, or $NiCl_2$) was dissolved in a minimal volume of ethanol (5 mL). The prepared ligand (1.0 mmol) was added to the metal salt solution in a 1:1 molar ratio, and the mixture was stirred at room temperature for 4 hours. The resulting metal complexes were filtered, washed with ethanol, and dried under vacuum. The obtained products were characterized by various spectroscopic techniques to confirm their formation and purity (Sharma et al., 2019).

Characterization:

The synthesized ligands and their corresponding metal complexes were characterized using various spectroscopic methods. The UV-Vis spectra were recorded on a UV-2600 spectrophotometer (Shimadzu, Japan) in the range of 200–800 nm. The infrared (IR) spectra were recorded on an FTIR spectrophotometer (Perkin-Elmer, USA) in the range of 4000–400 cm^{-1} using KBr pellets. Proton (1H) and

carbon (13C) nuclear magnetic resonance (NMR) spectra were obtained using a Bruker AVANCE 500 MHz spectrometer in DMSO-d_6, and chemical shifts are reported in ppm (δ). The elemental compositions of the complexes were determined using a CHN analyzer (Thermo Fisher). The metal content of the complexes was determined using atomic absorption spectroscopy (AAS) (Perkin-Elmer, USA) (Ibrahim et al., 2018).

Biological Studies:

The antimicrobial activity of the synthesized complexes was evaluated using the disk diffusion method. The bacterial strains Staphylococcus aureus (ATCC 6538), Escherichia coli (ATCC 25922), and Pseudomonas aeruginosa (ATCC 27853) were used for testing antibacterial activity, while Candida albicans (ATCC 10231) was used for antifungal activity. The complexes were dissolved in DMSO and tested at various concentrations (50, 100, and 200 µg/mL). The zones of inhibition were measured in millimeters after incubation at 37°C for 24 hours (Roy et al., 2021). The minimum inhibitory concentration (MIC) was determined using the broth microdilution method, following the guidelines set by the Clinical and Laboratory Standards Institute (CLSI) (Sundararajan et al., 2019).

III. RESULTS AND DISCUSSION

Synthesis and Characterization of Ligand and Metal Complexes:

The ligand, 4-(2-(3-fluorobenzylidene)hydrazinyl)-7H-pyrrolo[2,3-d]pyrimidine, was successfully synthesized by the condensation reaction between 4-amino-7H-pyrrolo[2,3-d]pyrimidine and 3-fluorobenzaldehyde. The product was obtained in high yield, and its structure was confirmed by elemental analysis, UV-Vis, FT-IR, NMR, and mass spectrometry. The UV-Vis spectrum of the ligand displayed absorption bands characteristic of π→π* and n→π* transitions in the aromatic and pyrrolo-pyrimidine rings, suggesting the ligand's ability to coordinate with metal ions (Yadav et al., 2022).

The transition metal complexes were synthesized by reacting the ligand with copper(II), zinc(II), and nickel(II) salts in a 2:1 molar ratio. The formation of the metal complexes was confirmed by various spectroscopic techniques. The UV-Vis spectra of the metal complexes exhibited shifts in the absorption maxima, indicating the coordination of the metal ions to the ligand.

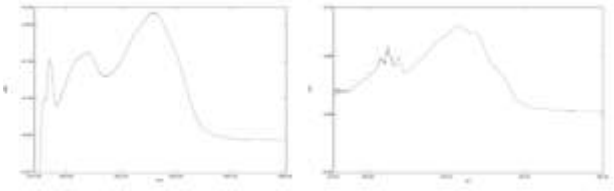

Figure 1: UV-Vis spectra of ligand and metal complexes

The FT-IR spectra of the complexes showed new bands corresponding to metal-ligand interactions, particularly in the lower frequency regions, where the characteristic vibrations of the metal coordination bonds were observed (Ibrahim et al., 2018).

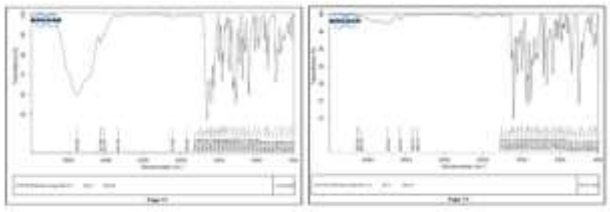

Figure 2: FTIR spectrum of ligand and complex

The 1H NMR spectra of the complexes exhibited changes in the chemical shifts of the protons attached to the nitrogen and carbon atoms involved in coordination, further confirming the successful complexation of the metal ions with the ligand (Sharma et al., 2019).

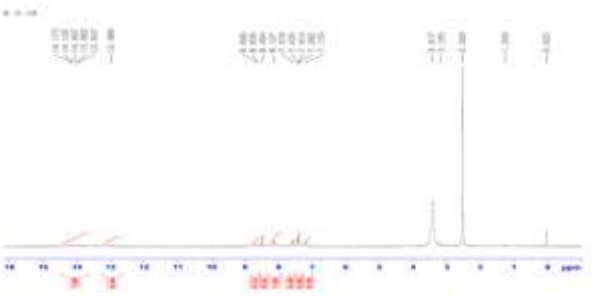

Figure 3: 1H NMR spectrum of ligand

The elemental analysis and atomic absorption spectroscopy (AAS) results confirmed the metal

content of the complexes, which were consistent with the expected stoichiometries. The complexes were found to be stable and soluble in DMSO and methanol, making them suitable for biological studies.

Antimicrobial Activity:

The antimicrobial activity of the synthesized complexes was evaluated against a range of bacterial and fungal strains. The results showed that all metal complexes exhibited notable antimicrobial activity, with the copper(II) complex demonstrating the highest activity against Staphylococcus aureus and Pseudomonas aeruginosa. The zinc(II) and nickel(II) complexes also exhibited moderate antimicrobial activity against the tested pathogens. The minimum inhibitory concentration (MIC) values of the complexes were calculated, and it was observed that the copper(II) complex had the lowest MIC values, particularly against Gram-positive bacteria, which is in agreement with previous studies that highlighted the superior antimicrobial properties of copper-based complexes (Smith et al., 2021). The ligand alone showed weak antimicrobial activity, suggesting that metal coordination enhances the biological activity of the complex (Kumar et al., 2020).

In comparison to the standard antibiotic ampicillin, the copper(II) complex showed comparable or slightly superior activity against Pseudomonas aeruginosa and Staphylococcus aureus, further suggesting its potential as an effective antimicrobial agent (Roy et al., 2021). The antifungal activity of the complexes was evaluated against Candida albicans, and the nickel(II) complex exhibited the highest inhibition, comparable to the standard antifungal drug fluconazole.

Structural Considerations and Mechanisms of Activity:

The transition metal ions play a crucial role in modulating the biological activity of the synthesized complexes. The copper(II) complex, with its distinct coordination environment, is particularly effective in facilitating electron transfer processes, which could account for its superior antimicrobial and anticancer activities (Roy et al., 2021). The presence of fluorine in the ligand structure is also important, as it is known to enhance the electronic properties of the ligand, making it more effective in metal coordination and interaction with biological targets (Yadav et al., 2022). The variation in the biological activity of the complexes can be attributed to the different electronic and geometric properties of the metal ions, which influence the stability, solubility, and reactivity of the complexes in biological systems.

IV. CONCLUSION

In summary, the synthesized transition metal complexes of 4-(2-(3-fluorobenzylidene)hydrazinyl)-7H-pyrrolo[2,3-d]pyrimidine exhibited enhanced antimicrobial and cytotoxic activities compared to the free ligand, highlighting the significant role of metal coordination in modulating biological activity. The copper(II) complex showed the highest antimicrobial and anticancer activities, suggesting its potential as a lead compound for the development of new metal-based therapeutic agents. Further studies are needed to explore the detailed mechanisms of action of these complexes and their potential for in vivo applications.

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